



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/54, 47/26, 47/38, 47/40		A1	(11) International Publication Number: WO 99/09988
			(43) International Publication Date: 4 March 1999 (04.03.99)
(21) International Application Number: PCT/EP98/05456			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 27 August 1998 (27.08.98)			
(30) Priority Data: 97114816.8 27 August 1997 (27.08.97) EP			
(71) Applicant (for all designated States except US): HEXAL AG [DE/DE]; Industriestrasse 25, D-83607 Holzkirchen (DE).			
(72) Inventors; and (75) Inventors/Applicants (for US only): STRUENGMANN, Andreas [DE/DE]; Industriestrasse 25, D-83607 Holzkirchen (DE). FREUDENSPRUNG, Brigitte [DE/DE]; Industries- trasse 25, D-83706 Holzkirchen (DE). KLOKKERS, Karin [DE/DE]; Industriestrasse 25, D-83607 Holzkirchen (DE).			
(74) Agents: BOETERS, Hans, D. et al.; Bereiteranger 15, D-81541 Muenchen (DE).			Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: NEW PHARMACEUTICAL COMPOSITIONS OF MELOXICAM WITH IMPROVED SOLUBILITY AND BIOAVAILABILITY			
(57) Abstract <p>Pharmaceutical compositions containing enolic carboxamide type antiinflammatory agent meloxicam that exhibit improved wettability, aqueous solubility, dissolution behaviour over a broad range of pH, and that are prepared by crystal structure modification of the drug through dry or wet mechanical homogenization with two further components – one of them is selected from a group of oligo – and dissolution improving, or alkalinizing agent. The application of the formulations according to the present invention results in an improved bioavailability and effectiveness of meloxicam.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

New Pharmaceutical Compositions of Meloxicam with Improved Solu-
bility and Bioavailability

Field of the invention:

The present invention relates to new pharmaceutical compositions of meloxicam having improved solubility and bioavailability and pharmaceutical formulations.

Background of invention:

Non-steroidal anti-inflammatory drugs (NSAID) are widely used for the long-term treatment of chronic rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The target enzyme for the action of NSAIDs is cyclooxygenase (COX), the rate-limiting enzyme of prostaglandin synthesis. Meloxicam [2H-1,2-benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl) -1,1-dioxide] is a new, enolic-acid type, non-steroidal antiinflammatory drug, with high antiinflammatory potency and low ulcerogenic activity and low renal toxicity. Be-

sides the effective antiinflammatory, antipyretic and analgesic activity (cyclo-oxygenase inhibitor, with relative COX-2 selectivity) of meloxicam it has been shown, that it prevents the development of colorectal cancer.

It is known, that meloxicam is crystallized in four different prototropic forms, the anion, the acidic enol, the zwitterion, and the cationic form, depending upon the pH value of the solution. Meloxicam has a low solubility in acidic or neutral medium. Therefore the preparation of pharmaceutical formulations results in complicated and difficult production processes. Furthermore the low solubility of meloxicam leads to unsteady resorption and consequently to non-uniform plasma levels in vivo.

JP 04321624 discloses the improvement of bioavailability of numerous non-steroidal antiinflammatory agents (e.g. indomethacin, fentanyl, flurbiprofen, piroxicam, lornoxicam and meloxicam) by formulating the drugs with styrene-isoprene-styrene block polymer and with crotamiton. An improved drug transdermal delivery is achieved in this way.

WO 93/01814 discloses ophthalmic meloxicam containing compositions for treating ocular inflammation and microbial infections. It describes instillable ophthalmic compositions of medium viscosity contain an anti-inflammatory oxicam as active ingredient, together with a gelling acrylic acid polymer and a base, such that the resultant aqua solution has the desired fluidity and an pH between 6,5 and 8.

IT 01251650 discloses an inclusion complex of meloxicam with cyclodextrin. The molar ratio of meloxicam to cyclodextrin is 1:2,5 claiming a real inclusion complex. The methods described

in the patent application are energy- and time consuming traditional techniques for complexing meloxicam.

Summary of the invention:

Main object of the present invention is to provide new compositions of meloxicam with improved solubility and bioavailability.

It has now surprisingly been found, that the solubility and bioavailability of meloxicam can be improved by mixing meloxicam with special additives using different production processes (co-milling, co-grinding, co-kneading etc.). It has further been found, that it is possible to produce special dosage forms containing meloxicam, resulting from the improved solubility.

Thus, the problem underlying the invention is solved by mixing meloxicam with additives like surfactants and/ or co-solvents and/ or hydrotropic agents and/ or alkalizing agents and/ or cyclodextrins and/ or hydrocolloids and/ or pharmaceutically acceptable polymers.

In one embodiment of the invention meloxicam is mixed with surfactants, especially polyoxyethylensorbitan-mono-fatty acids, diethylenglycolmonoethylether and nonylphenoltetraethylenglycolether.

In a further embodiment of the invention the solubility and bioavailability of meloxicam can be improved by micronisation of the substance in the presence of suitable co-solvents like propylenglycol, glycerol, polyethylenglycol and ethanol.

The addition of hydrotropic agents to meloxicam during micronisation can also improve solubility and bioavailability. Preferred hydrotropic agents are for example sodium-glycinate, nicotinamide, methylglucamin or a combination thereof.

The use of cyclodextrin in combination with meloxicam can improve the solubility and bioavailability without forming a real inclusion complex of cyclodextrin and meloxicam.

Suitable cyclodextrins are for example β -cyclodextrin hydrate (BCDx), 6-mono-amino-beta-cyclodextrin (AMBCDx), γ -cyclodextrin hydrate (GCDx), branchend- β -cyclodextrin (glycosyl-maltosyl-substituted type, enzyme-modified β -cyclodextrin hydrate derivative) and hydroxypropyl- β -cyclodextrin (with a degree of hydroxyalkylation between 4.0- 5.0).

Cyclodextrins are used preferably in an amount of meloxicam : cyclodextrin = 1 : 99 and especially 30 : 70 (w/w).

Combinations of the cyclodextrin meloxicam product with above mentioned additives result in further improvement of solubility and bioavailability.

Suitable additives are surfactants, co-solvents, hydrotropic components, alkalizing additives, hydrocolloids and pharmaceutically acceptable polymers, especially methyl-cellulose-propylene-glycol ether, tris-hydroxymethyl-aminomethane, 2,6-diamino-hexanoic acid (D,L-lysine), mannitol, polyethyleneglycol, propyleneglycol, diethanolamine, ethylenamine, monoethanolamine, triethanolamine, diisopropylamine, dibutylamine, pentylamine, sodium-carbonate, sodium dodecyl sulfate, ammonium-carbonate,

powdered sodium-hydroxide, sodium-phosphate, methylglucamine, polyvinylpyrrolidone, celluloseether, polyoxyethylen-polyoxypropylen-blockcopolymers and/ or nicotinamide.

Another object of the present invention is to provide pharmaceutical compositions containing meloxicam with the mentioned additives having improved solubility for oral, rectal, transdermal, ophthalmic and parenteral administration.

Another object of the present invention is to provide a controlled release oral pharmaceutical composition consisting a two-layer tablet. The first layer contain an initial rapid release dose of meloxicam together with at least one additive mentioned above. The second layer consists of meloxicam with usual pharmaceutical excipients respectively controlled release agents.

The auxiliary agents known in the state of the art are used for the preparation of these two-layered tablets.

Other pharmaceutical compositions of the present invention provide an effervescent tablet, flavored effervescent sachets, tablets, tabs, hydrogels, ophthalmic ointments, ophthalmic hydrogels and rectal suppositories.

Figure 1:

Heat flow curves of free meloxicam (a) the physical mixture of meloxicam with β -cyclodextrin hydrate (B) and of the composition according to example IV/1 (C).

Figure 2:

Heat flow curves of free meloxicam (a) the physical mixture of meloxicam with β -cyclodextrin hydrate (B) and of the composition according to example IV/2 (C).

Figure 3:

Heat flow curves of free meloxicam (A) the physical mixture of meloxicam with β -cyclodextrin hydrate (B) and of the composition according to example IV/3 (C).

Figure 4:

Heat flow curves of free meloxicam (A) the physical mixture of meloxicam with β -cyclodextrin hydrate (B) and of the composition according to example IV/4 (C).

In order to describe the invention more specifically but without intending to limit the scope of the invention in any way the following examples are presented:

Example I/1.

10 g meloxicam and 90 g microcrystalline cellulose (AVICEL) were intensively co-ground for 6 hours at room temperature in a ceramic ball mill in presence of 0.25 % (w/w) of the following surfactants:

TWEEN-80 and Solutol HS 15. The co-ground system was then dried to constant weight and passed through a 0.075 mm sieve.

The in vitro dissolution test shows that the composition according to example I/1 have significantly enhanced dissolution (table 1). The control composition consists of cellulose and meloxicam and was prepared under identical conditions as the surfactant-meloxicam-cellulose compositions.

Table 1. *In vitro dissolution of meloxicam (at pH 7.6, 37°C) from solid cellulose-based compositions after a 6-hour mechanical treatment.*

sample	dissolved meloxicam (in µg/ml)			
	5. min.	15. min	30. min.	45. min.
control	115	225	280	478
Tween-80	130	255	324	550
Solutol	145	280	400	590

Similar effects of the mentioned additives to the dissolution rates of meloxicam were observed at pH 6.6 in distilled water and at pH 1.2 in hydrochloric acid.

Example II./1.

25 g meloxicam were thoroughly milled in a ceramic ball mill at 25 °C for 6 hours with 75 g microcrystalline cellulose in presence of 5% (v/w) propylene glycol, polyethyleneglycol-400 (PEG-400) and glycerol, respectively. The composition was dried at 45 °C for constant weight yielding 102 g of slightly yellow solid with a meloxicam content of 24.6%. Dissolution-rates were determined in aqueous solution with pH 7.6 at 37 °C. The improvement of the dissolution rate of meloxicam due to the mechanical treatment is shown in table 2. (Control composition was prepared under identical mechanical treatment of 25 g meloxicam and 75 g microcrystalline cellulose without co-solvents.)

Table 2. Effect of co-solvents on the meloxicam dissolution in pH 7.6 buffer at 37 °C .

cosolvent	dissolved meloxicam in µg/ml			
	5.min.	15. min.	30.min.	45. min.
control	120*	231	379	490
PEG 400	305	355	480	580
prop.glycol	290	360	460	550

Example III/1.

25 g meloxicam and 75 g lactose were intensively co-ground in a ball mill for 4 hours without (control) and in presence of 20% (by weight) of nicotinamide and 20% of sodium-glycinate, respectively. The solid compositions were sieved through a 0.071 mm sieve and tested for meloxicam dissolution at pH=1.2 at 37 °C. Results are listed in table 3.

Table 3. Effect of hydrotropic additives to the meloxicam dissolution rate in pH 1.2 buffer at 37°C.

hydrotropes	dissolved meloxicam in µg/ml			
	5.min.	15. min.	30.min.	45. min.
control	0.20*	0.70	0.76	0.75
Na-glycinate	0.60	0.75	0.80	0.80
nicotinamide	0.80	0.85	0.98	0.90

Example IV/1.

The co-grinding of the solid components meloxicam and beta-cyclodextrin hydrate (BCDx) in a ceramic ball-mill for sufficient time results at ambient temperature in novel type solid state-structure of these solids, as proved by X-ray diffractometry and also by microscopy. The composition after grinding process also exhibited an improved dissolution profile compared to meloxicam, ground alone under the same conditions.

Thus 11.35 g crystalline beta-cyclodextrin hydrate (BCDx) with 13.8 % water content and 1.76 g crystalline meloxicam were intensively ball-milled for 6 hours at 25 °C to reach metastable amorphous state. The resulting solid composition was passed through a sieve of 250 µm.

Characteristics of the meloxicam composition according to example IV./1.: The product appears as a slightly yellow, free-flowing, non-hygroscopic powder.

As high resolution Differential Scanning Calorimetry investigations indicate this composition shows two distinct endothermic peaks -related to meloxicam -on the heat-flow curve at 255 °C, 280 °C. This phenomenon is attributed most probably to the co-existence of different solid state prototropic forms of the drug which are generated by the mechanical manipulation in presence of the hydrated beta-cyclodextrin. The DSC of pure meloxicam shows a melting endothermic heat flow at 267-270 °C which is in good agreement with literature data of the melting point of meloxicam (268°C).(See figure 1.)

The meloxicam content of the composition according to example IV/1. is 13.1% and the product has a loss of weight between 5.9-6.6 % after the drying. The X-ray powder diffraction analysis of the ball milled co-ground system according to example IV/1. indicates that the micronisation treatment results in the decrease of crystallinity, but without complete amorphisation of the system.

The dissolution characteristics of the meloxicam composition according to example IV/1. is shown in table 4.

The following standard method was used for the determination of the dissolution rate of the drug compositions: In vitro dissolution properties of the cyclodextrin based meloxicam compositions were studied under non-sink conditions in two different buffer systems, pH 1.3 and 7.6, respectively and in deionised water (pH=6.6) at 37 °C.

The stirring rate was 160 r.p.m.. To ensure comparable particle size distribution the samples were passed through a sieve of 80 mesh prior to dissolution testing. Sampling time intervals were 5, 10, 15, 30, 45 and 60 minutes.

Table 4.: In vitro rates of dissolution of free meloxicam and of the composition according to example IV./1. at pH 1.3 and 7.6 at 37°C

Dissolved meloxicam in solution in µg/ml				
minutes	free meloxicam		composition according to example IV/1.	
	pH: 1.3	pH: 7.6	pH:1.3	pH:7.6
5	0.30	38	2.5	975
10	0.38	218	2.6	981
15	0.44	320	2.7	1026
30	0.56	390	2.8	1046
45	0.59	485	2.7	1091
60	0.65	550	3.9	1117

The solubility enhancement at gastric pH was about 5-fold.

Example: IV/2.

1.0 g meloxicam, 9.0 g beta-CD hydrate (BCDx), 0.01g Methocel® and 5 ml of deionised water were added to a ceramic mortar and were intensively co-kneaded for 45 minutes at room temperature. The wet homogenisate was passed through a 2 mm sieve and dried at 40 °C yielding a hard, yellowish solid. The dry product was sieved through a 0.25 mm sieve. (9.53 g, meloxicam content: 8.7 % by weight.)

The solid state investigation of the product according to example IV/2. by DSC revealed the existence of a novel type of structure of the active ingredient, which is characterized by DSC heat-flow curves at the temperature range of 160-320 °C. This indicates the co-existence of two different allotropic forms of meloxicam, evidenced by negative enthalpy changes (melting) at around 250 and 293 °C respectively. None of these enthalpy changes are identical with the sharp melting heat flow of meloxicam itself that appears at 264-266°C. The simple mechanical mixture of meloxicam with beta-CD hydrate resulted in a composition that had a DSC pattern with a melting range (255-265°C)near the melting point of meloxicam. (See Figure 2.)

Dissolution characteristics of the product according to example IV/2. are shown in table 5.

Table 5.: *In vitro* rates of dissolution of free meloxicam (130 mg) and of the composition according to example IV./2. (1500 mg) at pH 1.3 and 7.6, 37°C.

Dissolved meloxicam in solution in µg/ml				
min- utes	free meloxicam		composition according to example IV/2.	
	pH: 1.3	pH: 7.6	pH:1.3	pH:7.6
5	0.45	38	7.4	917
10	0.62	218	7.8	990
15	0.67	320	7.7	1067
30	0.74	390	7.7	1077
45	0.73	485	7.9	1149
60	0.67	550	6.4	1199

Example: IV/3.

1.0 g meloxicam, 9.0 g of beta-CD hydrate (BCDx), 0.01g of tris-hydroxymethyl-aminomethane and 5 ml of deionised water were added to a twin-screw kneader and were intensively co-kneaded for 45 minutes at room temperature. The wet homogenisate was passed through a 2 mm sieve and dried at 40 °C yielding a hard, yellowish extrudate. The dry, solid product was sieved through a 0.25 mm sieve. (Yield: 10.03 g yellow powder, meloxicam content: 8.9 % by weight.)

The DSC pattern of the product according to example IV./3. showed the co-existence of two different allotropic forms of meloxicam with the characteristic negative enthalpy changes of 256 and 294 °C. (See figure 3.)

Dissolution characteristics of the product according to Example IV/3. in comparison with free meloxicam are shown in table 6.

Table 6.: In vitro rates of dissolution of free meloxicam (130 mg) and of the composition according to example IV./3. (1500 mg) at pH 1.3 and 7.6 at 37°C

Dissolved meloxicam in solution in µg/ml				
min-utes	free meloxicam		composition according to example IV/3.	
	pH: 1.3	pH: 7.6	pH:1.3	pH:7.6
5	0.45	38	6.8	1237
10	0.62	218	6.1	1252
15	0.67	320	5.9	1278
30	0.74	390	6.7	1280
45	0.73	485	6.1	1287
60	0.67	550	5.2	1310

Example: IV/4.

1.0 g meloxicam, 9.0 g of beta-CD hydrate (BCDx), 0.01g 2,6-diamino-hexanoic acid (DL-lysine) and 5 ml deionised water were added to a twin-screw kneader and were intensively co-kneaded for 45 minutes at room temperature. The wet mixture was dried at 40 °C yielding a hard, yellowish solid. The dry, solid product was sieved through a 0.25 mm sieve. (Yield: 9.9 g yellow powder, with a meloxicam content of 9.8 % by weight.)

Thermoanalytical study proved the existence of two different types of solid forms of meloxicam with melting heat flow curves at around 256 and 292°C respectively. (See figure 4.)

The improvement of dissolution characteristics of the product according to example IV/4. in comparison with free meloxicam are shown in table 7.

Table 7.: *In vitro* rates of dissolution of free meloxicam (130 mg) and of the composition according to example IV./4. (1300 mg) at pH 1.3 and 7.6 at 37°C

Dissolved meloxicam in solution in µg/ml				
min-utes	free meloxicam		composition according to example IV/4.	
	pH: 1.3	pH: 7.6	pH:1.3	pH:7.6
5	0.45	38	6.9	1134
10	0.62	218	4.8	1150
15	0.67	320	4.9	1160
30	0.74	390	4.9	1175
45	0.73	485	4.3	1187
60	0.67	550	4.6	1217

Example IV/5.

15.2 g 6-mono-amino-beta-cyclodextrin (AMBCDx), 3 ml water and 1.8 g crystalline meloxicam were intensively kneaded for 60 minutes at 25 °C. The resulting wet mixture was passed through a 2 mm sieve and dried at 40 °C to constant weight. The resulting yellowish solid was milled into a fine powder and sieved through a 0.25mm sieve. Yield: 16.6 g powder with a meloxicam content of 10.4 % by weight.

The solid meloxicam composition according to example IV/5. showed significantly improved dissolution.

The improved dissolution of meloxicam composition according to example IV/5. is shown in table 9.

Table 9.: The in vitro rate of dissolution of meloxicam composition according to example IV/5. (pH:1.2, at 37 °C)

minutes	meloxicam (µg/ml)
5	7.7
10	9.0
30	9.2
45	9.5
60	9.5*

* control: meloxicam showed a dissolution rate of 0.8 µg/ml at 60 min.

Example IV/6.

113.5 g solid, dry beta cyclodextrin hydrate (BCDx) are mixed thoroughly with 35.14 g crystalline meloxicam at 25°C in a high-speed twin-screw kneader for 10 minutes. 7.43 g polyethyleneglycol (PEG-400) are added to the kneading machine. The reaction mixture is thoroughly kneaded for 0.5 hours at 60°C, then for 2 hours at 25 °C. The resulting composition is directly transferred into a granulating machine and the granulation process is performed in the presence of 10 ml of a 0.1% aqueous sodium-carboxymethyl-cellulose solution. The granules are dried at 40 °C to constant weight.

The resulting free-flowing, slightly yellow granules can be used directly for tabletting.

Yield: 155 g granule, with a meloxicam content of 22.0%.

Example IV/7.

129.7 g crystalline gamma-cyclodextrin (GCDX) hydrate are intensively co-milled at room temperature in a ceramic ball mill with 17.57 g solid meloxicam for 3 hours at 25 °C. Yield: 146.2 g of slightly yellow, powder is obtained. The solid composition appears as a nearly amorphous powder with a meloxicam content of 11.8 % by weight and exhibits an enhanced dissolution in water.

Example IV/8.

16 g branched-beta-cyclodextrin (a glucosyl-maltosyl-substituted type, enzyme-modified beta-CDx derivative) are intensively kneaded in a twin-screw kneader with 1.8 g meloxicam in presence of 2.0 ml propyleneglycol for 30 minutes at 40 °C until a dense creamy paste is obtained. The paste is kneaded further for additional 3 hours at 25 °C, and dried at room temperature to constant weight. The dry product appears as a slightly yellow-coloured, hard solid which is further ground to give a fine powder and passed through a 250 µm sieve. Yield: 17.5 g yellow, slightly hygroscopic, amorphous powder, with a meloxicam content of 10.0 %. The loss of weight by drying of the sample according to example 8. is 6,0 %.

Example IV/9.

16 g hydroxypropyl-beta-cyclodextrin (with a degree of hydroxyalkylation between 4.0-5.0) are intensively mixed in powder form in a ceramic ball mill with 1.8 g of meloxicam. The mixture is then further co-milled for 3 hours at 25 °C to reach desired metastable physical state. Yield: 17.2 g yellowish,

amorphous powder, meloxicam content:10.0%. The drying loss of the product according to example IV/9. is 4.3 % and the sample appears to be amorphous by powder X-ray diffraction.

Example IV/10.

4.54 g beta cyclodextrin hydrate (BCDx) are wetted with 1 ml water and kneaded in a ceramic mortar with 0.702 g crystalline meloxicam at 25 °C for 15 minutes. Then 0.24 g solid nicotinamide are added to the mixture and the three-component solid system is further kneaded for 30 minutes at 25 °C. The mixture is dried at 45 °C to constant weight. Yield: 5.1 g of slightly yellow powder, with a meloxicam content of 11.9 % by weight. The composition according to example IV/10. shows significantly improved dissolution rates in a pH 7.6 buffer at 25 °C compared to meloxicam.

(See table 11.)

Table 11.: In vitro rates of dissolution of free meloxicam and of the composition according to example IV/10. at pH 1.3 and 7.6 at 37°C

Dissolved meloxicam in solution in µg/ml				
minutes	free meloxicam		composition according to example IV/10.	
	pH: 1.3	pH: 7.6	pH:1.3	pH:7.6
5	0.4	38	7.2	880
10	0.6	188	10	900
15	0.7	320	12	1100
30	0.7	390	12	1246
45	0.7	485	14.7	1391
60	0.6	550	13.9	1388

Example IV/11.

10.5 g beta-cyclodextrin-hydrate were mechanically treated by intense co-grinding with 1.6 g solid meloxicam and 1.5 g diethanolamine for 30 minutes at 40 °C, and for 2 hours at 25 °C. The resulting slightly yellow mixture was dried at 45 °C to constant weight and passed through a 0.071mm sieve. The obtained solid composition had a meloxicam content of 11.9 % by weight. The dissolution rate of the composition according to example IV/12. is shown in table 13.

Table 13.: In vitro dissolution of free meloxicam and of the composition according to example IV/12. at pH 1.3 and in deionised water (pH=6.6) at 37°C

Dissolved meloxicam in solution in µg/ml				
minutes	free meloxicam		Composition according to example IV/12.	
	pH: 1.3	pH: 6.6	pH:1.3	pH:6.6
5	0.4	23	8.0	700
10	0.6	148	8.3	626
15	0.7	232	9.6	659
30	0.7	390	10.1	780
45	0.7	415	10.0	896
60	0.6	475	12.1	940

The use of other pharmaceutically acceptable amines with a high boiling point (like ethylenediamine, monoethanolamine, triethanolamine, di-isopropylamine, dibutylamine, pentylamine etc.) and of other pharmaceutically acceptable solid alkalizing agents (like sodium-carbonate, ammonium-carbonate, powdered sodium-hydroxide, sodium-phosphate, etc.) resulted in improved solubility and bioavailability.

Example IV/12.

113.5 g solid, beta cyclodextrin hydrate (BCDx) are intensively co-milled in a ceramic ball mill with high energy with 35.14 g crystalline meloxicam and 0.5g sodium carbonate at 25 °C for 30 minutes.

Yield: 147.6 g slightly yellow, free-flowing powder with a meloxicam content of 22.0%. The solid composition appears to be almost amorphous by powder X-ray diffraction.

Example V/1.

Formulation of aromatised sachets equivalent to 7,5 mg meloxicam as active ingredient.

Meloxicam composition according to example IV/1.	58 mg
Sucrose	788 mg
Orange flavour granulate	14,5 mg
Ascorbic acid	7,25 mg
Methylglucamin	2,0 mg

Example V/2.

Preparation of an immediate releasing tablet containing 7,5 mg meloxicam per tablet.

Meloxicam composition according to example IV/1	58 mg
Lactose 1 H ₂ O	531 mg
Maize starch	251 mg
PVP XL	100 mg
Aerosil 200	50 mg
Magnesium Stearate	10 mg

Example V/3.

A 10 mg/g meloxicam hydrogel formulation is prepared as follows:
Micronised meloxicam composition according to example IV/9.,
equivalent to 10 mg of meloxicam 100,0 mg
Hydroxypropylmethylcellulose 215,0 mg

Propylenglycol	2500,0 mg
PEG-7-glyceryl-coconat	300,0 mg
Isopropylalcohol	500,0 mg
Deionised water	6385,0 mg

Example V/4.

Ophthalmic ointment:

In a Diosna cream-homogeniser a previously sterilized meloxicam composition according to example IV/12. is thoroughly mixed for 60 minutes with ophthalmic cream base at 25 °C having the following ingredients:

Aqua destillata	29.0 g
Cera flava	16.0 g
Paraffin subliquidum	48.0 g
Calcium stearinicum	4.5 g
Meloxicam composition according to example IV/13	2.5 g

Example V/5.

Preparation of an ophthalmic hydrogel.

The ophthalmic hydrogel formulation is prepared by dispersing meloxicam-composition according to example IV/4.

Water with 0.002 % thiomersal	95 g
Carbopol® 940	0.9 g
Diisopropanolamine	1.0 g
Meloxicam-composition according to example IV/4.	3.1 g

Example V/6.

Preparation of a rectal suppository.

The rectal suppository is prepared by mixing meloxicam-composition according to example IV/7. at 40°C with a previously molten hydrophilic suppository base consisting of Massa polyoxaetheni base. The composition of suppositories is 15 mg of meloxicam per suppository. Thus 127 mg of meloxicam-composition according to example IV/7. is mixed with 1873 mg of Massa polyoxaetheni base resulting in a 2 g suppository.

Example V/7.

Preparation of a two-layered tablet

In a first step the tableting mass for the initial dose is prepared. The components of the initial dose are:

Meloxicam-cyclodextrin (equivalent to 2,5 mg meloxicam)	19,1 mg
Lactose 1 H ₂ O	11,5 mg
Calcium hydrogen phosphate 2 H ₂ O	15,3 mg
Microcrystalline cellulose	18,7 mg
Maize starch	7,6 mg
Sodium starch glycollate	3,0 mg
Colloidal anhydrous silica	0,4 mg
Magnesium stearate	0,8 mg
Red ferric oxide	0,04 mg

They are sieved through a 0,8 mm sieve and homogenised in a container mixer for 20 min./ 5 rpm.

In a second step the granules for the controlled release layer are prepared. Meloxicam (5 mg), lactose 1 H₂O (56,3 mg), methyl-

hydroxypropylcellulose (12,5 mg), Crospovidone (2 mg) are granulated with purified water in a fluid bed granulator

Magnesium stearate(0,375 mg), colloidal anhydrous silica (0,25 mg) and sodium lauryl sulphate (0,125 mg) are added. The mixture is sieved through a 1,0 mm sieve and mixed in a container mixer for 20 min/ 5 rpm.

The slow release granules of above are compressed in a first run and the granules of the initial dose are added onto the controlled release layer and compressed as a second layer.

Example V/8.

Preparation of an effervescent tablet containing 7,5 mg meloxicam per tablet.

Meloxicam composition according to example IV/1	58 mg
Methylglucamin	2 mg
Sodium hydrogen carbonate	260 mg
Sodium hydrogen tartrate	320 mg
Aspartame	35 mg
Flavoring substances	77 mg

Example V/9.

Preparation of an effervescent tablet containing 7,5 mg meloxicam per tablet (3,142g).

Meloxicam composition according to example IV/1	58 mg
Lactose 1 H ₂ O	1102 mg
Docusate Sodium	5,8 mg
Polydimethylsiloxane	16,24 mg

Polyvinylpyrrolidone	37,7 mg
Citric acid	942,5 mg
Sodium hydrogen carbonate	333,5 mg
Sodium sulfate	348 mg
Saccharin Sodium	8,7 mg
Aspartame	58 mg
Flavoring agents	87 mg

Example V/10.

Preparation of a tablet containing 7,5 mg meloxicam per tablet.

Meloxicam composition according to example IV/1	58 mg
Lactose 1 H ₂ O	490,1mg
Microcrystalline Cellulose	145 mg
Crospovidone	23,2 mg
Magnesium Stearate	4,35 mg
Colloidal Anhydrous Silica	2,5 mg
Sodium Lauryl Sulfate	1,45 mg

The disclosure comprises also that of the attached application
EP 97 114 816.8.

Patent Claims

1. Pharmaceutical composition comprising meloxicam as active ingredient, an oligosaccharide and/or a polysaccharide, one or more pharmaceutically acceptable additives selected from the group consisting of

- surfactants,
- hydrotropic agents,
- alkalizing agents,
- hydrocolloids and
- polymers

and facultative excipients, carriers and/or auxiliary agents.

2. Composition according to claim 1, **characterized** by cyclodextrins, microcrystalline cellulose, lactose and/or starch as oligo- or polysaccharide.
3. Composition according to claim 1 or 2, **characterized** by polyoxyethylene-sorbitan-mono-fatty acid, diethyleneglycol monoethylether and /or nonylphenol tetraethyleneglycol ether as surfactant.
4. Composition according to any of the preceding claims, **characterized** by an amount of 1 to 99 and preferably about 20% by weight of a hydrotropic agent (based on the total weight of the composition).
5. Composition according to any of the preceding claims, **characterized** by sodium glycinate, nicotinamide and/or methylglucamine as hydrotropic agent.
6. Composition according to any of the preceding claims, **characterized** by sodium carbonate, ammonium carbonate, sodium hydroxide, especially powdered sodium hydroxide, and/or sodium phosphate as alkalizing agent.
7. Composition according to any of the preceding claims, **characterized** by β -cyclodextrin hydrate (BCDx), 6-monoamino-beta-cyclodextrin (AMBCDx), gamma-cyclodextrin hydrate (GCDx), branched β -cyclodextrin, especially a branched β -cyclodextrin of the glycosyl/maltosyl substituted type or a β -cyclodextrin hydrate derivative, and/or hydroxypropyl-

β -cyclodextrin as oligo- or polysaccharide, especially of a hydroxyalkylation degree in the range of 4.0 to 5.0.

8. Composition according to any of the preceding claims, **characterized** by methylcellulose-propylene-glycol ether, tris-hydroxymethylaminomethane, 2,6-diamino-hexanoic acid (D,L-lysine), mannitol, polyethyleneglycol, propyleneglycol, diethanolamine, ethyleneamine, monoethanolamine, triethanolamine, diisopropylamine, dibutylamine, pentylamine, sodium dodecylsulfate, methylglucamine, polyvinylpyrrolidone, cellulose ether, polyoxyethylene-polyoxypropylene-block-copolymers and/or nicotinamide as pharmaceutically acceptable additive.
9. Composition according to any of the preceding claims, obtainable by co-milling, co-grinding or co-kneading meloxicam in the presence of a pharmaceutically acceptable additive.
10. Composition according to any of the preceding claims, obtainable by micronizing meloxicam in the presence of a pharmaceutically acceptable additive.
11. Composition according to any of the preceding claims, obtainable by wet mechanical homogenization of its components in the presence of water, preferably in an amount of 5 to 50 % by weight (based on the total weight of the composition).
12. Pharmaceutical composition comprising meloxicam as active ingredient, as oligosaccharide and/or a polysaccharide, water as aqueous vehicle, a co-solvent and facultative auxiliary agents.
13. Composition according to claim 12, **characterized** by

cyclodextrins microcrystalline cellulose, lactose and/or starch as oligo- or polysaccharide.

14. Composition according to claim 12 or 13, **characterized** by an amount of 0.1 to 25 and preferably about 5.0 % by weight co-solvent (based on the amount of water or on the total weight of the composition).
15. Composition according to any of claims 12 to 14, **characterized** by i-propanol, propyleneglycol, glycerol, polyethyleneglycol and/or ethanol as co-solvent.
16. Composition according to any of claims 12 to 15, **characterized** by an amount of 1 to 99 and preferably about 20% by weight of a hydrotropic agent (based on the total weight of the composition).
17. Composition according to any of claims 12 to 16, **characterized** by one ore more additional pharmaceutical acceptable additives selected from the group consisting of surfactants, hydrotropic agents, alkalizing agents, cyclodextrins, hydrocolloids and polymers, preferably selected from the group consisting of methylcellulose-propylene-glycol ether, tris-hydroxymethylaminomethane, 2,6-diamino-hexanoic acid (D,L-lysine), mannitol, polyethyleneglycol, propyleneglycol, diethanolamine, ethyleneamine, monoethanolamine, triethanolamine, diisopropylamine, dibutylamine, pentylamine, sodium carbonate, sodium dodecylsulfate, ammonium carbonate, sodium hydroxide, especially powdered sodium hydroxide, sodium phosphate, methylglucamine, polyvinylpyrrolidone, cellulose ether, polyoxyethylene-polyoxypropylene-block-copolymers and/or nicotinamide as pharmaceutically acceptable additive.

18. Composition according to any of claims 12 or 17, obtainable by micronizing meloxicam in the presence of an oligosaccharide and/or polysaccharide, water and a co-solvent as pharmaceutically acceptable additive.
19. Composition according to any of the preceding claims, obtainable by wet mechanical homogenization of its components in the presence of water, preferably in an amount of 5 to 50 % by weight (based on the total weight of the composition).
20. Composition according to any of the preceding claims for oral, rectal, transdermal, ophthalmic or parenteral administration.
21. Composition according to any of the preceding claims, **characterized** in that it is provided as tablet, effervescent tablet, sachet, aromatized effervescent sachet, tab, hydrogel, ophthalmic ointment, ophthalmic hydrogel or rectal suppository.
22. Composition according to any of the preceding claims, **characterized** in that it is provided as controlled release tablet for oral application.
23. Composition according to claim 21 or 22, **characterized** in that it is provided as multi-layer tablet, especially a two-layer tablet, wherein
- one of the layers comprises meloxicam together with at least one pharmaceutically acceptable additive for rapid release and

- another layer comprises meloxicam optionally with a usual controlled release agent.

1/4

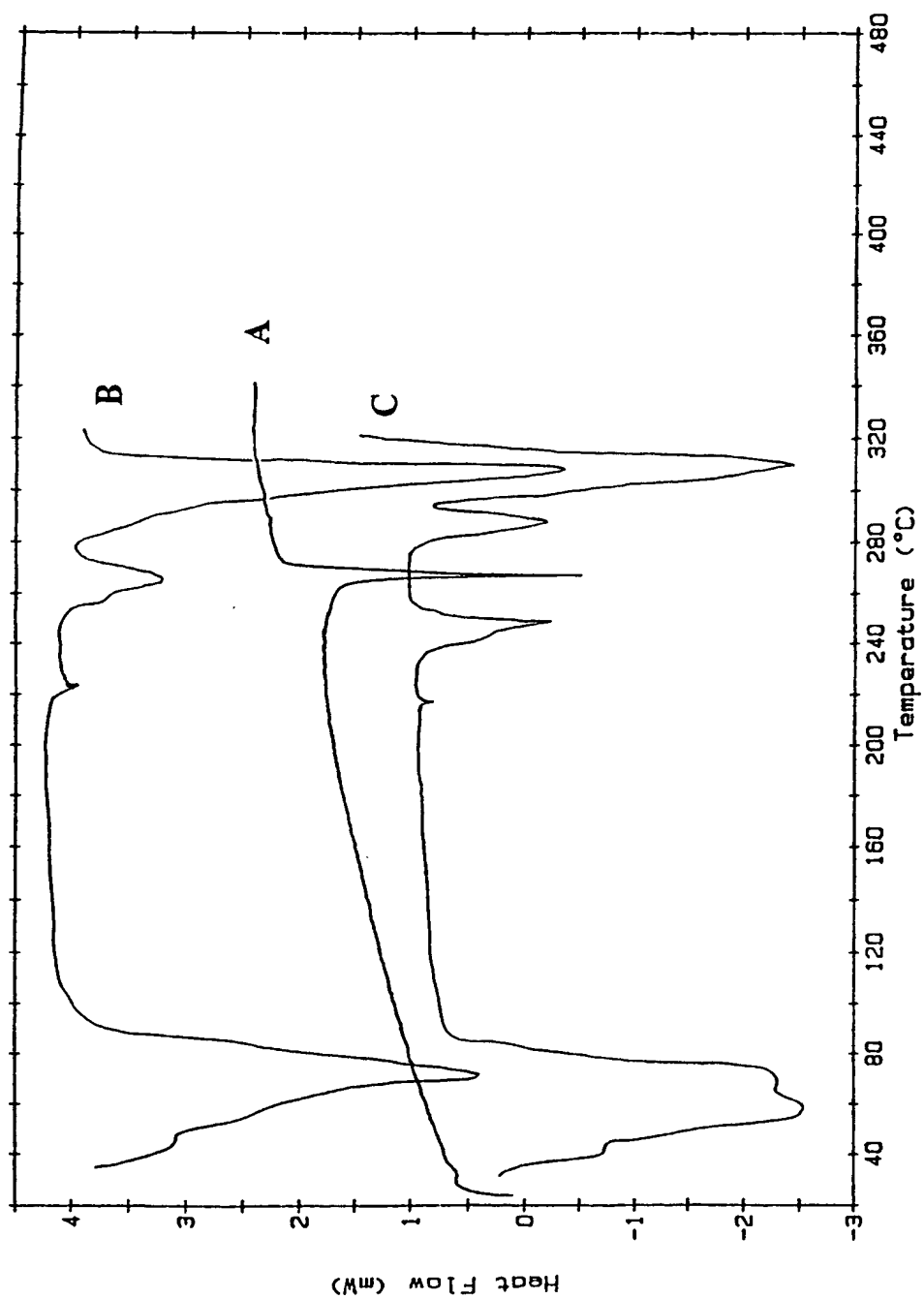
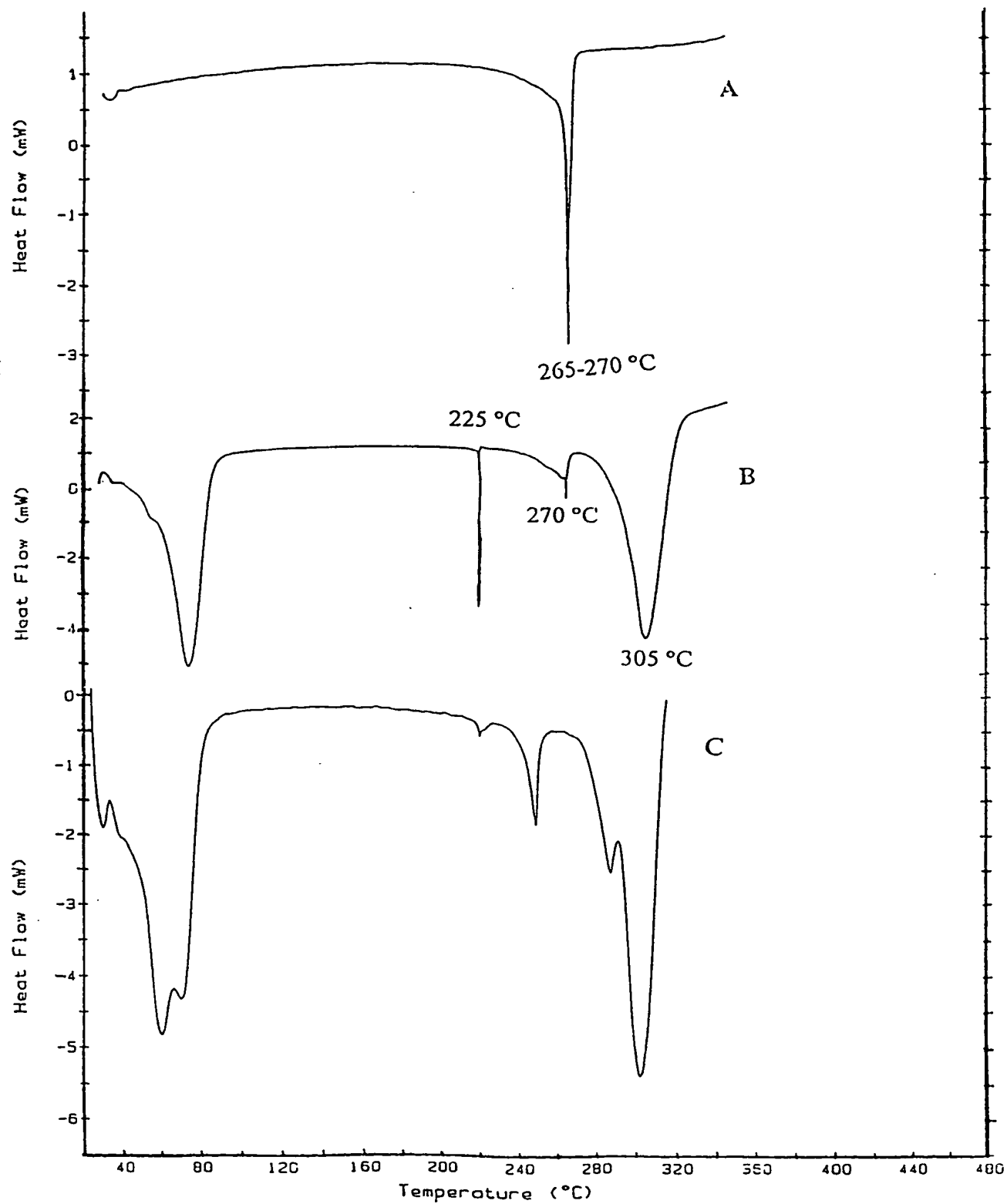


Fig. 1

2 / 4

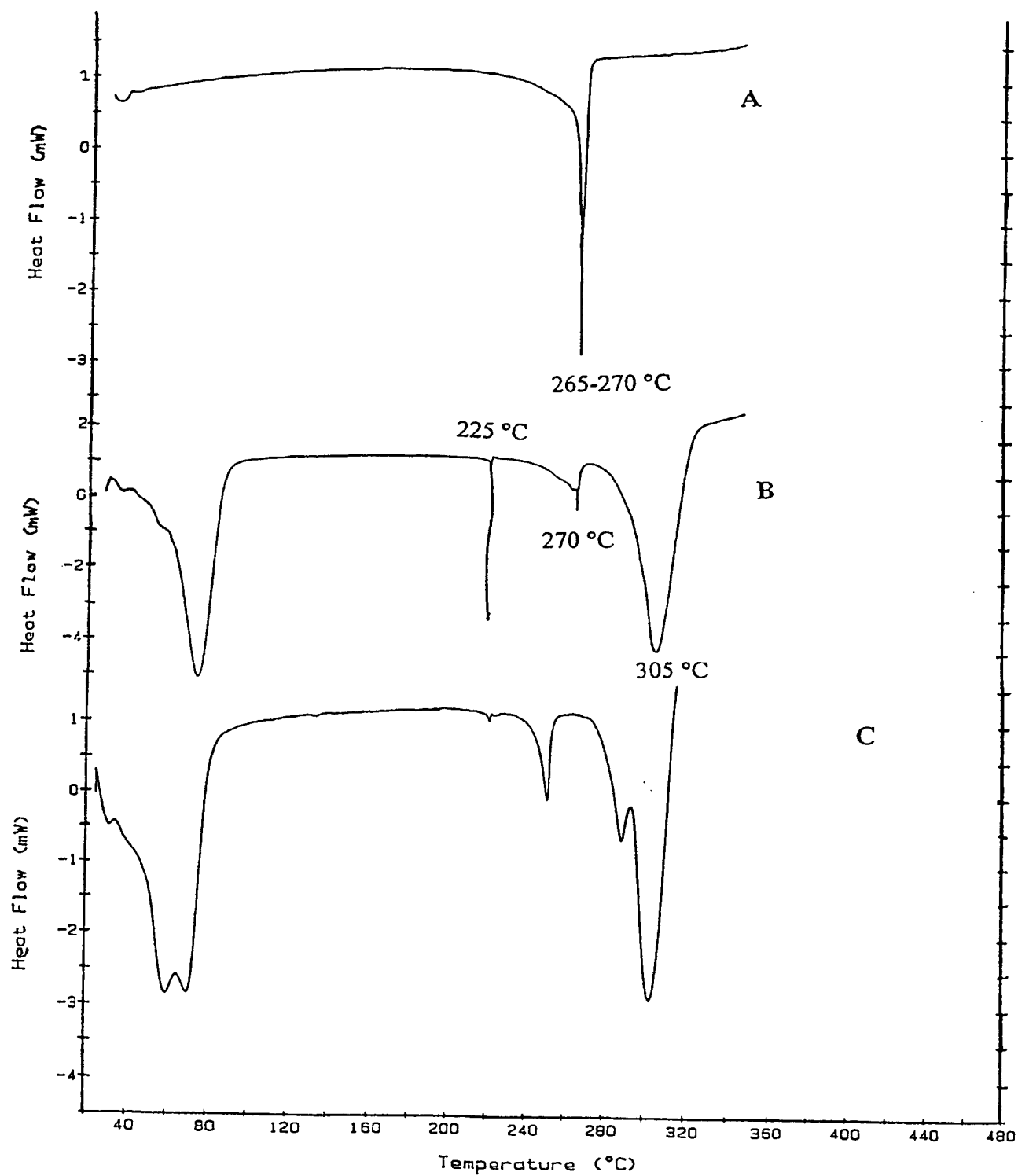
Fig. 2



SUBSTITUTE SHEET (RULE 26)

3 / 4

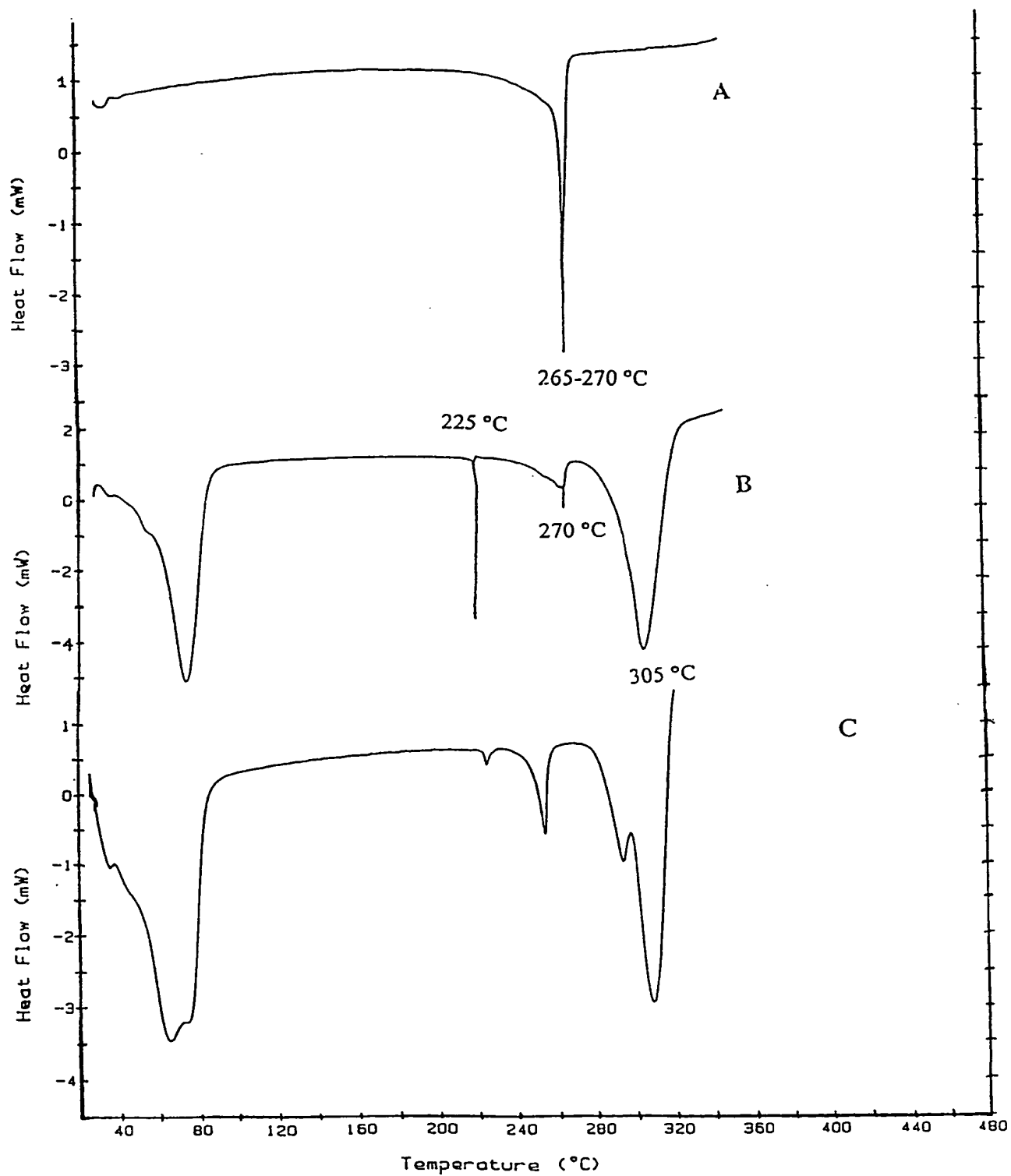
Fig. 3



SUBSTITUTE SHEET (RULE 26)

4 / 4

Fig. 4



SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/05456

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/54 A61K47/26 A61K47/38 A61K47/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE WPI Week 9548 Derwent Publications Ltd., London, GB; AN 95-368773 '48! XP002087683 cited in the application see abstract & IT 1 251 650 B (BOEHRINGER INGELHEIM ITAL. S.P.A., IT) 17 May 1995</p> <p style="text-align: center;">--- -/--</p>	1-23

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

14 December 1998

Date of mailing of the international search report

29/12/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Scarponi, U

INTERNATIONAL SEARCH REPORT

Int .tional Application No

PCT/EP 98/05456

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 118, no. 18, 3 May 1993 Columbus, Ohio, US; abstract no. 175803, XP002087682 cited in the application see abstract & JP 04 321624 A (HISAMITSU PHARMACEUTICAL CO. INC.,JP) 11 November 1992 ----	1-23
A	EP 0 002 482 A (KARL THOMAE) 27 June 1979 see claims 1-3,9 see examples ----	1-23
A	WO 93 01814 A (LABORATOIRE EUROPHTA) 4 February 1993 cited in the application see the whole document ----	1-23
A	WO 97 03667 A (MERCK) 6 February 1997 see claims 1,3 see page 19, line 19 - page 22, line 29 ----	1-23
A,P	WO 97 31631 A (RPMS) 4 September 1997 see claims 18-26 see page 21, line 28 - page 23, line 16 -----	1-23

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/05456

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 002482	A	27-06-1979	DE 2756113 A	21-06-1979
			AT 365589 B	25-01-1982
			AT 863078 A	15-06-1981
			AU 522538 B	10-06-1982
			AU 4253078 A	21-06-1979
			BG 33286 A	14-01-1983
			BG 60475 B	28-04-1995
			CA 1102802 A	09-06-1981
			CS 9104100 A	17-06-1992
			CS 202515 B	30-01-1981
			DD 140354 A	27-02-1980
			DK 562078 A,B,	17-06-1979
			FI 783867 A,B,	17-06-1979
			GR 65626 A	15-10-1980
			IE 48042 B	05-09-1984
			JP 1474086 C	27-12-1988
			JP 54092976 A	23-07-1979
			JP 63024997 B	23-05-1988
			LU 88557 A	21-03-1995
			MX 9202949 A	01-07-1992
			US 4233299 A	11-11-1980
WO 9301814	A	04-02-1993	FR 2679135 A	22-01-1993
			AT 147627 T	15-02-1997
			AU 2388392 A	23-02-1993
			DE 69216831 D	27-02-1997
			DE 69216831 T	31-07-1997
			DK 594770 T	21-07-1997
			EP 0594770 A	04-05-1994
			ES 2099272 T	16-05-1997
			FI 940224 A	14-03-1994
			NO 940160 A	04-03-1994
WO 9703667	A	06-02-1997	AU 6496096 A	18-02-1997
			CZ 9800156 A	16-09-1998
			EP 0839034 A	06-05-1998
			NO 980221 A	18-03-1998
WO 9731631	A	04-09-1997	CA 2183217 A	28-08-1997

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)